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PLASMA AND URINARY LACTATE FOR DIAGNOSIS OF EARLY ONSET SEPSIS IN NEONATES

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ABSTRACT

Background: Monitoring tissue perfusion in sepsis is essential for the early detection of circulatory failure, timely initiation of appropriate interventions, and assessment of therapeutic response. Inadequate oxygen delivery leads to elevated lactate levels, which have been shown to predict morbidity and mortality in newborns. However, limited research has explored the role of lactate measurements in the diagnosis and prognosis of neonatal sepsis. **Aim:** To determine the minimum threshold levels of plasma and urinary lactate useful for diagnosing early-onset sepsis (EOS). **Materials and Methods:** This study included ninety neonates at risk for EOS. Sepsis screening, blood culture, plasma lactate (within the first two hours of life), and urinary lactate (from the first urine sample) were assessed. At 24 ± 2 hours of life, repeat measurements of C-reactive protein (CRP), plasma lactate, and urinary lactate were obtained. **Results:** In the sepsis group, the median urinary lactate levels in the first urine sample and at 24 hours were 0.50 mMol/L and 0.45 mMol/L, respectively. In the non-sepsis group, the corresponding values were 0.37 mMol/L and 0.43 mMol/L. Neither plasma nor urinary lactate levels were reliable for diagnosing EOS. However, urinary lactate at 24 hours demonstrated utility as a diagnostic marker for sepsis associated with shock and mortality. **Conclusion:** Plasma and urinary lactate levels do not predict EOS. Nonetheless, urinary lactate measured at 24 hours of life may serve as an indicator for shock and mortality in infants with EOS.

Key words: Sepsis, urinary, lactate

INTRODUCTION

Early-onset neonatal sepsis (EOS) results from bacterial pathogens transmitted from the mother to the infant before or during delivery, and it typically presents within the first 72 hours of life. Timely diagnosis of EOS remains challenging. The management of neonates born at risk of EOS depends on maternal and neonatal risk factors, sepsis screening parameters performed after birth, and clinical symptoms.[1,2] Although blood culture remains the gold standard for confirming neonatal sepsis, its turnaround time of at least 48 hours often leads to the administration of intravenous antibiotics to many uninfected infants. To reduce unnecessary antibiotic exposure, a sensitive, specific, and easily accessible early diagnostic marker is needed. To date, no single ideal biomarker has been identified that can accurately diagnose septicaemia and guide effective antibiotic therapy.

Lactate has been widely used as a marker of hypoxia and impaired tissue perfusion in various neonatal and pediatric conditions.[3,4] Urinary lactate has shown diagnostic value in disorders such as hypoxic-ischemic encephalopathy and bronchopulmonary dysplasia,[5,6] but its utility in neonatal sepsis has not been explored.

Neonatal sepsis is a systemic condition caused by bacterial, viral, or fungal pathogens and is associated with significant morbidity and mortality. Its incidence ranges from 1 to 5 per 1000 live births, depending on the population studied and case definitions.[7] Clinical manifestations vary widely, from subtle signs to severe systemic involvement. Infectious agents may originate from maternal or intrauterine flora, though community- or hospital-acquired organisms may also be responsible. Based on the timing of symptom onset, neonatal sepsis is categorized into early-onset, late-onset, and very-late-onset forms. EOS typically refers to infections presenting within the first 72 hours, although some authors extend this window to 7 days. Late-onset sepsis occurs between day 4 and day 30 (or after day 7), while very-late-onset sepsis refers to cases identified in infants hospitalized in the neonatal intensive care unit from day 30 onward until discharge.[8,9]

Pathogens are commonly transmitted vertically from mother to infant. Microorganisms from the cervix, vagina, rectum, birth canal, or uterus may ascend across intact or ruptured membranes before or during labor, potentially causing chorioamnionitis.[10] In some cases, however, the presence of clinical signs and bacteremia at birth—especially in infants delivered via cesarean section without membrane rupture—suggests possible transplacental transmission.[11]

Because early diagnosis is difficult, management of neonates at risk of EOS relies on clinical assessment, sepsis screening results after birth, maternal and neonatal risk factors, and early laboratory findings.[12,13] Given the delay in obtaining blood culture results, many infants receive antibiotics unnecessarily. An early, reliable, and accessible laboratory marker for predicting EOS is therefore essential.[14]

Currently, no single biomarker reliably identifies neonatal septicaemia or guides antibiotic therapy with sufficient accuracy. Lactate serves as a marker of hypoxia and poor perfusion, and its measurement has diagnostic utility in several neonatal

conditions.[15] Urinary lactate, in particular, offers the advantages of being noninvasive and easy to obtain. Although it has shown usefulness in hypoxic-ischemic encephalopathy and bronchopulmonary dysplasia,[16,17] its role in neonatal sepsis remains unexplored. Additionally, no established urinary lactate threshold exists for diagnosing EOS.

Therefore, we designed this study with the primary aim of determining the threshold values of urinary lactate for diagnosing EOS in at-risk neonates using first-passed urine and at 24 ± 2 hours of life. A secondary aim was to determine the corresponding threshold values of plasma lactate at 2 hours and at 24 ± 2 hours after birth.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Paediatrics, Dr. KNS Memorial Institute of Medical Sciences, Barabanki, Lucknow, a tertiary care hospital. Neonates with **two or more risk factors for early-onset sepsis (EOS)** were enrolled after obtaining written informed consent from parents or legal guardians.

Exclusion criteria:
Neonates with birth asphyxia (Apgar score <7 at 1 minute), congenital anomalies, multiple gestations, meconium-stained amniotic fluid, infants of diabetic mothers (IDM), infants born to mothers with metabolic disorders, and those with other significant morbidities were excluded.

All enrolled neonates underwent a sepsis screen—absolute neutrophil count (ANC), total leukocyte count (TLC), micro-ESR, C-reactive protein (CRP), and immature-to-total neutrophil (I/T) ratio—along with blood culture and **plasma lactate measurement within the first two hours of life**. CRP and plasma lactate were repeated at **24 ± 2 hours**.

For urinary lactate estimation, **two urine samples** were collected: the **first-passed urine** and a second sample at **24 ± 2 hours** of life. Infants were monitored for clinical signs of sepsis and blood culture outcomes. Antibiotics were initiated in neonates with a positive sepsis screen, foul-smelling amniotic fluid, more than two EOS risk factors, or more than one significant antenatal risk factor.

Neonates were classified into three categories:

- **No sepsis:** absence of clinical signs with negative sepsis screen and negative culture.
- **Probable sepsis:** presence of clinical signs/symptoms with at least two abnormal laboratory markers.
- **Proven sepsis:** clinical signs/symptoms with a positive blood culture.
- **Sample size:** A convenience sample of 70 neonates was included.

Sample Collection

Using aseptic precautions, **3 mL of venous blood** was drawn through a heparinized cannula into a fluoride–oxalate vial for plasma lactate measurement. Plasma was

separated by centrifugation at 400 × g for 10 minutes within 30 minutes of collection and stored at −20°C until analysis.

Urine samples were collected using a perineal urine collection bag, and urine was aspirated using a sterile syringe. When this method was unsuccessful, a sterile urinary catheter was used.

Lactate Assay

Lactate levels in stored plasma and urine were measured within 24 hours using a colorimetric method with Lactate Multipurpose Liquid Reagent on automated or semi-automated analyzers.

The **primary objective** was to determine urinary lactate cut-off values in first-passed urine and at 24 ± 2 hours for diagnosing EOS in at-risk neonates.
The **secondary objective** was to determine plasma lactate thresholds at 2 hours and 24 ± 2 hours for diagnosing EOS.

Statistical Analysis

Data analysis was performed using **SPSS version 24.0**. A p-value ≤ 0.05 was considered statistically significant. Fisher's exact test was used to assess associations between blood culture results and categorical variables. Mean gestational age, anthropometric parameters, vital signs, ANC, TLC, micro-ESR, and I/T ratio were compared between blood culture–positive and blood culture–negative neonates using the unpaired Student's t-test.

The **Mann–Whitney U test** was used to compare median plasma and urinary lactate levels between:

- blood culture–positive and negative groups
- survivors and non-survivors
- infants with and without shock.

RESULTS

70 neonates who were born with two or more EOS risk factors were included in the study. Group 1 (sepsis) was assigned to neonates with a positive blood culture result; group 2 (non-sepsis) was assigned to those with a negative blood culture result.

Table 1: Comparison of Baseline Demographic Profile and Sepsis Screen Parameters of Neonates between Sepsis and Non-Sepsis Groups

Variables	**Group 1 (n = 8)**	**Group 2 (n = 62)**	P value
Male:female	4:4	37:25	0.74
Preterm:term	6:2	52:10	0.041
SGA:AGA	1:7	35:27	0.78
Anthropometry Mean (SD)			
Gestational age (weeks)	32.1	33.2	0.37
Birth weight(gm)	1785	1900.1	0.61

Length (cm)	40.4	42.7	0.32
Head circumference (cm)	30.8	31.4	0.71
Sepsis Screen Parameters			
TLC /cu mm (mean± SD)	17750±82.2	13630.7±110.6	0.0001
ANC /cu mm (mean± SD)	8627.8±114.5	8092.4±322.1	0.578
I/T ratio (mean ±SD)	0.04±0.02	0.067±0.02	0.001
Micro ESR (mm at 1st hr) (mean ± SD)	1.65±0.1	1.1±0.5	0.003
CRP Positivity n (%)			
At 2 HOL	1(12.5%)	4(6.5%)	0.24
At 24 HOL	3(37.5%)	9(14.5%)	

Table 2.Comparison of Median (IQR) of Urinary and Plasma Lactate between Sepsis and Non-Sepsis Groups Variables

	Group 1 (n = 8) Median (IQR)	**Group 1 (n = 62) Median (IQR)**
Urinary lactate in first passed sample	**0.61**	**0.41**
Urinary lactate at 24 Hours Of Life	**0.36**	**0.46**
Plasma lactate at 2 HOL	**2.73**	**2.66**
Plasma lactate at 24 HOL	**3.07**	**2.71**

Median (IQR) of urinary lactate and plasma lactate in first passed urine and at 24 hours in both groups were not able to diagnose culture-positive EOS.

Table 3: Comparison of Urinary and Plasma Lactate in Survivors vs Non-Survivors and with Shock and Without Shock

	Group 1 (n = 8) Median (IQR)	**Group 1 (n = 62) Median (IQR)**	**P-value**
Urinary lactate at 2 HOL	0.68	0.4	0.04
Urinary lactate at 24 HOL	0.96	0.58	0.0049
Plasma lactate at 2 HOL	2.88	2.76	0.74
Plasma lactate at 24 HOL	3.61	2.71	0.024
Variables	**Shock Present(n =8) Median (IQR)**	**Shock absent (n = 62) Median (IQR)**	
Urinary lactate at 2 HOL	0.55	0.55	0.16
Urinary lactate at 24 HOL	0.82	0.42	0.032
Plasma lactate at 2 HOL	3.4	3.4	0.74
Plasma lactate at 24 HOL	3.22	3.22	0.084

The baseline demographic characteristics of neonates in both groups are summarized in Table 1. The incidence of early-onset sepsis (EOS) was higher among preterm neonates compared with term neonates. Other baseline parameters were comparable between the groups. Mean I/T ratio, micro-ESR, ANC, and TLC did not differ significantly between the sepsis and non-sepsis cohorts.

Positive CRP levels were observed in 12.5% of infants at 2 hours and increased to 37.5% at 24 hours in Group 1. In Group 2, 6.5% of neonates had a positive CRP at 2 hours, rising to 14.5% at 24 hours. Although CRP positivity at 24 hours was higher in the sepsis group than in the non-sepsis group, the difference was not statistically significant. Respiratory and heart rates were also comparable between the two groups.

Respiratory distress was the most common clinical feature, occurring in 43% of culture-positive and 47% of culture-negative neonates. However, several clinical manifestations were more frequent in the sepsis group, including meningitis (8% vs. 1.5%), shock (32% vs. 6.4%), disseminated intravascular coagulation (28% vs. none), lethargy (18% vs. 6.4%), necrotizing enterocolitis (9% vs. 1%), pneumonia (27% vs. 3.1%), hypoglycemia (8% vs. 1.5%), feeding intolerance (21% vs. 4.5%), and mottling (9% vs. 1%).

Plasma and urinary lactate levels were compared between survivors and non-survivors. Non-survivors exhibited significantly higher median (IQR) urinary lactate levels both in the first-passed urine sample and at 24 hours compared with survivors. Plasma lactate levels and urinary output were also analyzed in infants who developed shock versus those who did not. A significant difference in median (IQR) urinary lactate levels at 24 hours was noted between infants with shock and those without shock.

Using a cutoff value of **0.42 mMol/L**, urinary lactate at 24 hours demonstrated **70% sensitivity** and **57.5% specificity** for identifying neonates who developed shock.

DISCUSSION

Lactate is widely recognized as a marker of tissue hypoperfusion and has consistently been shown to rise in septic patients. Earlier studies suggested that sepsis represents a pathological state of tissue hypoxia caused by disturbances in either macrocirculation or microcirculation.[18,19] Traditionally, elevated lactate levels were attributed to anaerobic metabolism secondary to inadequate oxygen delivery.[20] However, more recent evidence indicates that lactate elevation in sepsis cannot be explained solely by tissue hypoxia. Many septic patients demonstrate a hyperdynamic circulation with adequate tissue oxygenation. Increased metabolic demand in sepsis can enhance glycolytic flux, promoting the conversion of pyruvate to lactate through pyruvate dehydrogenase.[21]

Lactate elevation has also been linked to endogenous catecholamine surge. Elevated levels of epinephrine and norepinephrine have been reported in both humans and animal models of septic shock, and these catecholamines correlate strongly with hyperlactatemia. Precise reference ranges for lactate in neonates are not well defined. Hawdon et al.[22] demonstrated an association between postnatal age and plasma lactate trends in newborns. Newborns typically experience a decline in blood glucose immediately after birth, with stabilization occurring over the next 2–3 hours; this drop

is more pronounced in preterm infants.[23] This physiological pattern may explain the normal urinary and plasma lactate levels observed at 2 hours of life in our culture-positive neonates, most of whom were preterm.

Levraut et al.[24] and Bellomo et al.[25] have shown that elevated lactate levels in severe sepsis and septic shock are often due to impaired clearance rather than excess production. Notably, lactate clearance declines significantly only when hepatic blood flow is markedly reduced.[26] Since our septic neonates did not present with severe sepsis or septic shock at birth, this could account for their normal lactate values on day one. Beyond the liver, the renal cortex is the second major organ responsible for lactate metabolism through excretion, gluconeogenesis, and oxidation.[27] Renal excretion becomes significant only once lactate levels surpass the renal threshold (6–10 mMol/L).

In our study, urinary lactate levels were significantly elevated both in the first-passed urine and at 24 hours among infants who later developed shock. This finding is clinically important. Infants who maintain blood pressure through endogenous catecholamine-driven compensatory mechanisms may be in occult shock, and elevated lactate can serve as an early indicator of this state.[28] Because renal function was normal in all infants, we hypothesize that elevated urinary lactate reflects the excretion of excessive circulating lactate and therefore serves as a more sensitive marker than plasma lactate in detecting early hemodynamic compromise.

Although blood culture remains the gold standard for diagnosing EOS, its sensitivity is limited to 30–40%. Biomarkers such as procalcitonin and IL-6 have shown greater diagnostic potential but are not widely accessible for routine bedside use.[29] In contrast, lactate is an inexpensive, readily available bedside test. A notable strength of our study is that it evaluated lactate specifically in neonates with stable hemodynamics, unlike many adult and pediatric studies which focus predominantly on severe sepsis and shock.

However, the study had important limitations, including a relatively small sample size and a low rate of culture positivity. Larger studies with serial plasma and urinary lactate measurements beyond 24 hours are needed to more clearly define the role of lactate as a diagnostic and prognostic marker in EOS.

CONCLUSION

A noninvasive, rapid, and reliable biomarker is needed for diagnosing infants with risk factors for early-onset sepsis. In this study, plasma and urinary lactate levels at 2 and 24 hours of life did not distinguish between neonates with and without EOS. However, urinary lactate at 24 hours was a more accurate indicator of mortality and shock in at-risk infants compared with plasma lactate. These findings suggest that urinary lactate may serve as a useful prognostic marker in early-onset sepsis

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